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HOWREY LLP - DC
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DUNSTON, JENNIFER ANN	

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1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/660,893	LINK ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2007 and 03 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-21 and 26-34* is/are pending in the application.

4a) Of the above claim(s) *9,10,24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,11-21 and 26-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 May 2007* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 5/1/2007, in which claims 7, 22 and 23 were canceled, and claims 1-6, 8, 21, 27 and 29-32 were amended, and claims 33-34 were newly added. Currently, claims 1-6, 8-21 and 24-34 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected "SAVI" as the species of method step of determining the identity of the protein fused to the marker peptide, and "pGT-fs0" as the viral vector used in the step of introducing the polynucleotide into the genome of the host cell with traverse in the reply filed on 8/22/2006.

Claims 9, 10, 24 and 25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/22/2006.

Currently, claims 1-6, 8, 11-21 and 26-34 are under consideration.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or

more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application Nos. 09/811,842 (hereinafter the '842 application) and 60/190,678 (hereinafter the '678 application), fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The specifications of the prior-filed applications do not disclose the specific steps recited in the claimed method. The instant claims require the use of a construct comprising in a 5' to 3' orientation: i) a splice acceptor consensus sequence, ii) a complementary sequence of a first type IIS restriction enzyme recognition sequence, iii) an oligonucleotide sequence encoding an assayable marker peptide, iv) a sequence of a second type IIS restriction enzyme recognition sequence, and v) a splice donor consensus sequence. In the '842 application, the only reference to a vector that meets the structural limitations of the claims is found in Figure 2D. The specification describes this vector as a "transfection cassette" (e.g. page 9, paragraph 1). The '678 application fails to disclose any constructs that meet the structural limitations of the claims. Furthermore, the specification of the '842 application does not teach the method of SAVI where at least one type IIS restriction enzyme cleaves upstream and

downstream of the peptide marker sequence. The specification of the '842 application teaches that a restriction enzyme is used which cuts at a known site within one end of the expression construct (e.g. page 59, 1st full paragraph; depicted in Figure 17). Thus prior-filed applications do not disclose the specific steps required by the claims.

Accordingly, prior-filed Application Nos. 09/811,842 and 60/190,678 do not provide adequate support under 35 USC § 112, first paragraph, for claims 1-6, 8, 11-21 and 26-34.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/458,152 (hereinafter the '152 application), fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The disclosure of the '152 application fails to provide support for the sorting of cells into monoclonal subgroups of genetically identical cells. At page 32, lines 4-9, the specification of the '152 application teaches away from isolating each individual cell, and instead teaches the sorting of cells based upon their expression of the marker gene such that cells are grouped together by virtue of demonstrating an approximately equivalent level of marker gene expression. Instant claims 3, 5 and 28 require the step of sorting cells into monoclonal subgroups of genetically identical cells. The prior-filed application does not provide adequate support for this step.

Accordingly, prior-filed Application No. 60/458,152 does not provide adequate support under 35 USC § 112, first paragraph for claims 3, 5 and 28. Claims 8, 11-21, 26, 27 and 29-34 depend directly or indirectly from claims 3 or 5 and thus lack support in Application No. 60/458,152 for the same reasons as applied to claims 3 and 5.

In summary, claims 1, 2, 4 and 6 have an effective filing date of 3/27/2003 (the filing date of Application No. 60/458,152), and claims 3, 5, 8, 11-21 and 26-34 have an effective filing date of 9/12/2003 (the filing date of the instant application).

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

Figure 2k (Drawings submitted 5/1/2007) contains nucleotide sequences of ten nucleotides each that are not referred to by the use of a sequence identifier. Where the description or claims of a patent application discuss a sequence that is set forth in the Sequence Listing, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

In response to this office action, Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. The nature of the non-compliance did not preclude an examination of the elected invention on the merits, the results of which are presented below.

This is a new objection necessitated by the introduction of Figure 2k in the reply filed 5/1/2007.

Drawings

The drawings are objected to because figure 2k is not described in the specification. Figure 2G was missing in the originally filed application. In the amendment filed 6/24/2008 replacement drawings were submitted for Figures 2G-2J, and the specification was amended to refer to only Figures 2A-2J. In the reply filed 5/1/2007, Applicant has included Figure 2k, which is a duplicate of Figure 2J (except is does not contain the sequence identifier for the disclosed nucleic acid sequence). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Response to Arguments - Claim Objections

The previous objections of claims 1-6, 21-23 and 29-32 under have been withdrawn in view of Applicant's amendment to the claims in the reply filed 5/1/2007.

Response to Arguments - Double Patenting

The rejection of claims 1, 7, 8, 13-15, 19-21 and 23 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11, 15, 18-25, 29-35, 76, 77, 79 and 80 of copending Application No. 10/810,976 is moot in view of the abandonment of Application No. 10/810,976.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection, necessitated by the amendment of claims 29-32 and addition of claims 33-34 in the reply filed 5/1/2007.

Claim 29 recites the limitation "the restriction enzymes that cut at the non-Type IIS REs" in step (iv)(7). There is insufficient antecedent basis for this limitation in the claim. The structures used to perform the serial analysis of viral integration method of steps 1-9 originate in the vector used in the method of claim 1. The claims do not indicate that the vector contains

non-type IIS restriction enzyme sites. Furthermore, it is unclear whether the practice of step 4 has any effect on the serial analysis of viral integration process if it is performed after step 3. Step 3 requires "subjecting said cDNA to a Type IIS restriction enzyme (RE) that recognizes the first and second Type IIS restriction enzyme recognition (RER) sites." Step 4 requires "generating a cDNA fragment by cleaving the cDNA upstream of the first Type IIS RER site and downstream of the second Type IIS RER." The specification indicates that when the cDNA is subjected to Type IIS restriction enzyme that recognizes the first and second Type IIS RER sites, cleaving the cDNA upstream of the first Type IIS RER site and downstream of the second Type IIS RER site occurs (e.g., paragraph [0044]). Thus, the metes and bounds of the method are not clear in light of the description provided in the specification.

Claims 31 and 32 depend from claim 29 and thus are indefinite for the same reasons applied to claim 29.

Claim 30 recites the limitation "the restriction enzymes that cut at the non-Type IIS REs" in step (iv)(7). There is insufficient antecedent basis for this limitation in the claim. The structures used to perform the serial analysis of viral integration method of steps 1-9 originate in the vector used in the method of claim 1 or 2. The claims do not indicate that the vector contains non-type IIS restriction enzyme sites. Furthermore, it is unclear whether the practice of step 4 has any effect on the serial analysis of viral integration process if it is performed after step 3. Step 3 requires "subjecting said cDNA to a Type IIS restriction enzyme (RE) that recognizes the first and second Type IIS restriction enzyme recognition (RER) sites." Step 4 requires "generating a cDNA fragment by cleaving the cDNA upstream of the first Type IIS RER site and downstream of the second Type IIS RER." The specification indicates that when the cDNA is

subjected to Type IIS restriction enzyme that recognizes the first and second Type IIS RER sites, cleaving the cDNA upstream of the first Type IIS RER site and downstream of the second Type IIS RER site occurs (e.g., paragraph [0044]). Thus, the metes and bounds of the method are not clear in light of the description provided in the specification. Moreover, the preamble of the claim recites "The method of claims 1 or 2, wherein the generation of an assayable signal from the peptide marker requires interaction with other protein or protein fusions, said method comprising..." Claims 1 and 2 lack antecedent basis for the phrase "the generation of an assayable signal."

Claims 33 and 34 depend from claim 30 and thus are indefinite for the same reasons applied to claim 30.

Claim 32 recites the limitation "The method of screening for small molecule drugs" in line 1. There is insufficient antecedent basis for this limitation in the claim. The only method of screening for small molecule drugs is claim 28. However, claim 32 does not depend from claim 28, it depends from claim 29. Furthermore, claim 32 requires screening to be performed "in cells generated according to claim 29." However, claim 29 is not directed to a method of generating cells. Claim 29 is drawn to a method of identifying protein/protein interactions and not to a method of generating cells. Claim 29 encompasses the generation of cells comprising a fusion protein comprising a target protein and a first subunit of a reporter, and cells comprising a construct that has been randomly introduced into the genome in addition to the fusion protein comprising the target protein and first subunit of the reporter. It is unclear which cells of claim 29 are used in the method of claim 32. Thus, the metes and bounds of claim 32 are unclear.

Claim 34 recites the limitation "The method of screening" in line 1. There is insufficient antecedent basis for this limitation in the claim. The only method of screening for small molecule drugs is claim 28. However, claim 34 does not depend from claim 28, it depends from claim 30. Furthermore, claim 34 requires screening to be performed "in cells generated according to claim 30." However, claim 30 is not directed to a method of generating cells. Claim 30 encompasses the generation of cells comprising a fusion protein comprising a target protein and a first subunit of a reporter, and cells comprising a construct that has been randomly introduced into the genome in addition to the fusion protein comprising the target protein and first subunit of the reporter. It is unclear which cells of claim 30 are used in the method of claim 34. Thus, the metes and bounds of claim 34 are unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

Claim 8 requires the following steps to perform a method of serial analysis of viral integration (SAVI), where the method consists of the following steps: "i) isolating mRNA from each subgroup of cells; ii) reverse transcribing the mRNA into double stranded cDNA; iii)

subjecting the cDNA to a reaction with at least one enzyme that recognizes the type IIS restriction enzyme recognition sequences flanking the oligonucleotide encoding the peptide marker sequence, and cleaves the cDNA upstream of the first recognition sequence and downstream of the second recognition sequence, thereby generating one or more cDNA fragments, where each of these fragments comprise the oligonucleotide sequence corresponding to the upstream and downstream exons directly fused to the marker peptide encoding sequence; iv) self-ligating all cDNA fragments generated by digestion with said restriction enzyme; v) amplifying by the inverse polymerase chain reaction the fragments containing the oligonucleotide sequences of the exons fused to the marker peptide; vi) ligating these fragments together to form a concatenated molecule; vii) cloning and sequencing said concatenated molecules; and viii) comparing the sequence of each oligonucleotide against oligonucleotide sequences in a one or more nucleotide sequence database thereby identifying one or more fusion proteins present in each subgroup of cells." In the reply filed 5/1/2007, the claim was amended to insert the step of "ligating these fragments together to form concatenated molecules" and to require sequencing of the concatenated molecules.

The transitional phrase "consisting of" excludes any element, step or ingredient not specified in the claim. According to the method of claim 8, one must ligate the inverse PCR fragments together to form a concatenated molecule. However, the specification does not describe the process where inverse PCR products are concatenated. The specification describes additional steps between subjecting the restriction fragments to inverse PCR and forming a concatamer. Specifically, the specification describes the restriction digest of the inverse PCR product with non-type IIS restriction enzymes to cleave away the marker sequence (e.g.,

paragraph [0187]). The restriction enzyme digested PCR product free of marker sequence is then ligated to form a concatamer, which is then sequenced (e.g., paragraph [0187]). The direct ligation of inverse PCR produces to form a concatamer is not contemplated by the present specification as filed.

The original specification, drawings and claims were thoroughly reviewed and no support could be found for the amendment. Accordingly, the amendment is a departure form the specification and claims as originally filed.

Response to Arguments - 35 USC § 112

The previous rejection of claims 1, 3, 4, 7, 8, 11-23 and 26-28 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 5/1/2007.

The rejection of claim 22 under 35 U.S.C. 112, first paragraph, is moot in view of Applicant's cancellation of the claim in the reply filed 5/1/2007.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 12 and 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvik et al (US Patent No. 5,652,128; see the entire reference) in view of Smith (BioTechniques,

Vol. 23, No. 1, pages 116-120, 1997; see the entire reference), as evidenced by the 1996 New England Biolabs, Inc. Catalog, page 39. This rejection was made in the Office action mailed 11/2/2006 and is reiterated below.

Jarvik et al teach a method of tagging genes and proteins, comprising the steps of (1) randomly introducing a CD-DNA construct by nonhomologous recombination into the genome of eukaryotic cells, (2) identifying those cells that express the CD tagged protein, and (3) determining the sequence identity of the protein or nucleic acid to which the CD tag has been fused (e.g. column 8, line 20 to column 9, line 61; column 4, lines 9-20). Jarvik et al teach that the CD-DNA construct contains a splice acceptor and a splice donor flanking a peptide-encoding segment (e.g. Figure 2). The peptide-encoding segment may encode an epitope that is detected with an antibody by standard immunological techniques including immunofluorescence, which depends on the interaction of the antibody with the epitope, and immunocytochemical methods (e.g. column 9, lines 42-60). The peptide may be a peptide-encoding sequence that can be read in both directions or in multiple reading frames with the absence of a stop codon (e.g. paragraph bridging columns 8-9). The peptide is fused to an endogenous coding sequence and thus the initiation codon is that of the endogenous coding sequence and not the epitope tag (e.g. column 9, lines 40-60). Jarvik et al teach that the CD-DNA construct is introduced into the eukaryotic cells by a vector such as a plasmid or virus (e.g. column 8, lines 20-38). Jarvik et al do not specify the particular nucleotide sequences present in each segment of the CD-DNA construct and teach that there are many sequences that could serve and that could be used by one skilled in the arts of molecular biology (e.g. column 7, lines 8-12).

Jarvik et al do not teach the sequence of a CD-DNA construct containing (i) a complementary sequence of a first type IIS restriction enzyme recognition sequence and (ii) a second type IIS restriction enzyme recognition sequence, where the sequences are placed on either sited of an oligonucleotide sequence encoding an assayable marker peptide and within the splice acceptor and splice donor sites. Jarvik do not specifically teach the use of retroviruses to deliver the CD-DNA construct.

Smith teaches a mini-exon comprising in a 5' to 3' orientation: i) a splice acceptor consensus sequence (3'CS), (ii) the sequence GAGG, a sequence complementary to the MnlI type IIS restriction enzyme recognition sequence, (iii) an oligonucleotide encoding a myc epitope that does not provide the initiation codon and lacks a stop codon, (iv) the sequence CCTC, a MnlI type IIS restriction enzyme recognition sequence, and (iv) a splice donor (5'CS) (e.g. Figure 1; paragraph bridging pages 117-118). Further, Smith suggests the use of the mini-exon as a tool for gene discovery by placing the mini-exon into introns in a random fashion using retroviruses or bacterial transposons, which would permit the facile detection of proteins. Smith teaches that the mini-exon has the advantage of allowing greater speed of screening for new genes.

The 1996 New England Biolabs, Inc. Catalog (page 39) is cited only to show that the recognition sequence for MnlI is 5'-CCTCNNNNNNN-3'.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of protein tagging of Jarvik et al to include a retrovirus comprising the mini-exon cassette taught by Smith as the CD-DNA construct because Jarvik et al teach it is within the ordinary skill in the art to use a virus to deliver a variety of sequences that

can be identified and used by one skilled in the art, and Smith suggests the use of the mini-exon for random protein tagging.

One would have been motivated to make such a modification in order to receive the expected benefit of providing a specific sequence to be used in the method, which would be required to actually carry out the method taught by Jarvik, and to provide facile detection of proteins and a faster identification of new genes as taught by Smith. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1, 12, 14, 15 and 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvik et al (US Patent No. 5,652,128; see the entire reference) in view of Smith (BioTechniques, Vol. 23, No. 1, pages 116-120; see the entire reference) further in view of Morin et al (PNAS, Vol. 98, No. 26, pages 15050-15055, 2001; see the entire reference), as evidenced by the 1996 New England Biolabs, Inc. Catalog, page 39. This rejection was made in the Office action mailed 11/2/2006 and is reiterated below.

The teachings of Jarvik et al are described above and applied as before.

Jarvik et al do not teach the sequence of a CD-DNA construct containing (i) a complementary sequence of a first type IIS restriction enzyme recognition sequence and (ii) a second type IIS restriction enzyme recognition sequence, where the sequences are placed on either sited of an oligonucleotide sequence encoding an assayable marker peptide and within the splice acceptor and splice donor sites. Jarvik do not specifically teach the use of retroviruses to

deliver the CD-DNA construct. Jarvik et al do not teach the splice acceptor and splice donor flanking a green fluorescent protein coding sequence.

Smith teaches a mini-exon comprising in a 5' to 3' orientation: i) a splice acceptor consensus sequence (3'CS), (ii) the sequence GAGG, a sequence complementary to the MnlI type IIS restriction enzyme recognition sequence, (iii) an oligonucleotide encoding a myc epitope that does not provide the initiation codon and lacks a stop codon, (iv) the sequence CCTC, a MnlI type IIS restriction enzyme recognition sequence, and (iv) a splice donor (5'CS) (e.g. Figure 1; paragraph bridging pages 117-118). Further, Smith suggests the use of the mini-exon as a tool for gene discovery by placing the mini-exon into introns in a random fashion using retroviruses or bacterial transposons, which would permit the facile detection of proteins. Smith teaches that the mini-exon has the advantage of allowing greater speed of screening for new genes.

The 1996 New England Biolabs, Inc. Catalog (page 39) is cited only to show that the recognition sequence for MnlI is 5'-CCTCNNNNNNN-3'.

Morin et al teach the inclusion of an enhanced green fluorescent protein (EGFP) coding sequence into an artificial exon used for gene trapping, where the artificial exon contains a splice acceptor His tags, EGFP coding sequence and a splice donor in a 5' to 3' orientation (e.g. Figure 1). Morin et al teach that the inclusion of the EGFP coding sequence into the artificial exon is advantageous when used in gene trapping experiments, because the GFP coding sequence lacks initiation and stop codons and allows the fusion of GFP to the amino- and carboxyl-terminal parts of the trapped protein and allows the GFP coding sequence to be used to determine subcellular localization of the protein (e.g. page 15051, Results).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of protein tagging of Jarvik et al to include a retrovirus comprising the mini-exon cassette taught by Smith as the CD-DNA construct because Jarvik et al teach it is within the ordinary skill in the art to use a virus to deliver a variety of sequences that can be identified and used by one skilled in the art, and Smith suggests the use of the mini-exon for random protein tagging. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the mini-exon cassette of Smith et al to include the EGFP coding sequence of Morin et al, because both Smith et al and Morin et al teach the use of a mini-exon or artificial exon (i.e., a coding sequence flanked by a splice acceptor and splice donor) for gene trapping.

One would have been motivated to make such a modification in order to receive the expected benefit of providing a specific sequence to be used in the method, which would be required to actually carry out the method taught by Jarvik, and to provide facile detection of proteins and a faster identification of new genes as taught by Smith. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention. Further, one would have been motivated to include the EGFP coding sequence in order to receive the expected benefit of being able to determine the subcellular localization of the tagged protein.

Claims 1, 12, 14-21, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvik et al (US Patent No. 5,652,128; see the entire reference) in view of Smith

(BioTechniques, Vol. 23, No. 1, pages 116-120; see the entire reference) further in view of Morin et al (PNAS, Vol. 98, No. 26, pages 15050-15055, 2001; see the entire reference) and Sinclair (The Scientist, Vol. 15, No. 5, p. 23, 2001; see the entire reference), as evidenced by the 1996 New England Biolabs, Inc. Catalog, page 39. This rejection was made in the Office action mailed 11/2/2006 and is reiterated below.

The teachings of Jarvik et al are described above and applied as before.

Jarvik et al do not teach the sequence of a CD-DNA construct containing (i) a complementary sequence of a first type IIS restriction enzyme recognition sequence and (ii) a second type IIS restriction enzyme recognition sequence, where the sequences are placed on either sited of an oligonucleotide sequence encoding an assayable marker peptide and within the splice acceptor and splice donor sites. Jarvik do not specifically teach the use of retroviruses to deliver the CD-DNA construct. Jarvik et al do not teach the splice acceptor and splice donor flanking a green fluorescent protein (GFP) coding sequence, where the green fluorescent protein coding sequence is a humanized renilla GFP.

Smith teaches a mini-exon comprising in a 5' to 3' orientation: i) a splice acceptor consensus sequence (3'CS), (ii) the sequence GAGG, a sequence complementary to the MnlI type IIS restriction enzyme recognition sequence, (iii) an oligonucleotide encoding a myc epitope that does not provide the initiation codon and lacks a stop codon, (iv) the sequence CCTC, a MnlI type IIS restriction enzyme recognition sequence, and (iv) a splice donor (5'CS) (e.g. Figure 1; paragraph bridging pages 117-118). Further, Smith suggests the use of the mini-exon as a tool for gene discovery by placing the mini-exon into introns in a random fashion using retroviruses or bacterial transposons, which would permit the facile detection of proteins. Smith

teaches that the mini-exon has the advantage of allowing greater speed of screening for new genes.

The 1996 New England Biolabs, Inc. Catalog (page 39) is cited only to show that the recognition sequence for MnlI is 5'-CCTCNNNNNNN-3'.

Morin et al teach the inclusion of an enhanced green fluorescent protein (EGFP) coding sequence into an artificial exon used for gene trapping, where the artificial exon contains a splice acceptor His tags, EGFP coding sequence and a splice donor in a 5' to 3' orientation (e.g. Figure 1). Morin et al teach that the inclusion of the EGFP coding sequence into the artificial exon is advantageous when used in gene trapping experiments, because the GFP coding sequence lacks initiation and stop codons and allows the fusion of GFP to the amino- and carboxyl-terminal parts of the trapped protein and allows the GFP coding sequence to be used to determine subcellular localization of the protein (e.g. page 15051, Results).

Sinclair teaches that Stratagene's Vitality™ hrGFP mammalian expression vectors allow protein expression and subcellular localization studies similar to those using jellyfish (*Aquorea victoria*) GFP, except hrGFP is less toxic in many mammalian cells (e.g. page 1/3). Further, Sinclair teaches a construct comprising a FLAG or HA tag followed by an internal ribosomal entry site and an hrGFP coding sequence (e.g. page 2/3). Sinclair teaches that the construct comprising the IRES site allows for detection of the gene of interest by antibodies against FLAG or HA while expression can be monitored by hrGFP detection (e.g. page 2/3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of protein tagging of Jarvik et al to include a retrovirus comprising the mini-exon cassette taught by Smith as the CD-DNA construct because Jarvik et al

teach it is within the ordinary skill in the art to use a virus to deliver a variety of sequences that can be identified and used by one skilled in the art, and Smith suggests the use of the mini-exon for random protein tagging. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the mini-exon cassette of Smith et al to include a GFP coding sequence as taught by Morin et al, wherein the GFP coding sequence is hrGFP with or without the IRES sequence, because both Smith et al and Morin et al teach the use of a mini-exon or artificial exon (i.e., a coding sequence flanked by a splice acceptor and splice donor) for gene trapping and Morin et al and Sinclair teach the use of constructs to make GFP fusion proteins.

One would have been motivated to make such a modification in order to receive the expected benefit of providing a specific sequence to be used in the method, which would be required to actually carry out the method taught by Jarvik, and to provide facile detection of proteins and a faster identification of new genes as taught by Smith. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention. Further, one would have been motivated to include the hrGFP coding sequence in order to receive the expected benefit of being able to determine the subcellular localization of the tagged protein, as taught by Morn et al, when the IRES site is absent and to determine expression visually when the IRES site is present, as taught by Sinclair. Moreover, one would have been motivated to use the hrGFP coding sequence, because the protein is less toxic than jellyfish GFP in mammalian cells.

Claims 1, 2, 12 and 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvik et al (US Patent No. 5,652,128; see the entire reference) in view of Smith (BioTechniques, Vol. 23, No. 1, pages 116-120; see the entire reference) and Keeton et al. Biological Science. 5th Edition. New York: W.W. Norton & Company, Inc., 1993, p. 441), as evidenced by the 1996 New England Biolabs, Inc. Catalog, page 39. This rejection was made in the Office action mailed 11/2/2006 and is reiterated below.

The teachings of Jarvik et al are described above and applied as before. Further, Jarvik et al teach the application of the method to the analysis of cellular responses, where CD-tagging is used to identify proteins, and the genes encoding them, whose synthesis is stimulated by a particular treatment, such as the administration of a particular hormone or growth factor to a particular cell type by comparing treated (i.e., test group) and untreated cells (i.e., reference group) to identify proteins whose levels change in response to the treatment (e.g. column 4, lines 36-46).

Jarvik et al do not teach the sequence of a CD-DNA construct containing (i) a complementary sequence of a first type IIS restriction enzyme recognition sequence and (ii) a second type IIS restriction enzyme recognition sequence, where the sequences are placed on either sited of an oligonucleotide sequence encoding an assayable marker peptide and within the splice acceptor and splice donor sites. Jarvik et al do not specifically teach the use of retroviruses to deliver the CD-DNA construct. Jarvik et al do not specifically teach the use of statistical methods to identify proteins whose levels change among the test and reference groups.

Smith teaches a mini-exon comprising in a 5' to 3' orientation: i) a splice acceptor consensus sequence (3'CS), (ii) the sequence GAGG, a sequence complementary to the MnlI

type IIS restriction enzyme recognition sequence, (iii) an oligonucleotide encoding a myc epitope, (iv) the sequence CCTC, a MnlI type IIS restriction enzyme recognition sequence, and (iv) a splice donor (5'CS) (e.g. Figure 1; paragraph bridging pages 117-118). Further, Smith suggests the use of the mini-exon as a tool for gene discovery by placing the mini-exon into introns in a random fashion using retroviruses or bacterial transposons, which would permit the facile detection of proteins. Smith teaches that the mini-exon has the advantage of allowing greater speed of screening for new genes.

The 1996 New England Biolabs, Inc. Catalog (page 39) is cited only to show that the recognition sequence for MnlI is 5'-CCTCNNNNNNN-3'.

Keeton et al teach that scientists in all fields of research constantly encounter the same fundamental question—whether deviations that they observe in their experimental results occur by chance or are significant. Keeton et al teach that scientists cannot rely upon a guess and must use a system of standards based upon the mathematical probability that any observed deviation in their sample could have occurred by chance alone. Keeton et al teach that this type of analysis is called statistical analysis (page 441).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of protein tagging of Jarvik et al to include a retrovirus comprising the mini-exon cassette taught by Smith as the CD-DNA construct because Jarvik et al teach it is within the ordinary skill in the art to use a virus to deliver a variety of sequences that can be identified and used by one skilled in the art, and Smith suggests the use of the mini-exon for random protein tagging. Further, it would have been obvious to one of skill in the art at the time the invention was made to modify the method of protein tagging of Jarvik et al to include

the statistical analysis of the differences between the test and reference groups as taught by Keeton.

One would have been motivated to make such a modification in order to receive the expected benefit of providing a specific sequence to be used in the method, which would be required to actually carry out the method taught by Jarvik, and to provide facile detection of proteins and a faster identification of new genes as taught by Smith. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention. One would have been motivated to include statistical analysis of the data in order to receive the expected benefit of determining whether the result occurred by change or is statistically significant as taught by Keeton et al.

Claims 1, 2-6, 12, 13, 17-21 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvik et al (US Patent No. 5,652,128; see the entire reference) in view of Smith (BioTechniques, Vol. 23, No. 1, pages 116-120; see the entire reference), Keeton et al. Biological Science. 5th Edition. New York: W.W. Norton & Company, Inc., 1993, p. 441) and Whitney et al (US Patent No. 5,928,888, cited as reference A6 on the IDS filed 7/6/2004; see the entire reference), as evidenced by the 1996 New England Biolabs, Inc. Catalog, page 39. This rejection was made in the Office action mailed 11/2/2006 and is reiterated below.

The teachings of Jarvik et al are described above and applied as before. Further, Jarvik et al teach the application of the method to the analysis of cellular responses, where CD-tagging is used to identify proteins, and the genes encoding them, whose synthesis is stimulated by a

particular treatment, such as the administration of a particular hormone or growth factor to a particular cell type by comparing treated (i.e., test group) and untreated cells (i.e., reference group) to identify proteins whose levels change in response to the treatment (e.g. column 4, lines 36-46).

Jarvik et al do not teach the sequence of a CD-DNA construct containing (i) a complementary sequence of a first type IIS restriction enzyme recognition sequence and (ii) a second type IIS restriction enzyme recognition sequence, where the sequences are placed on either sited of an oligonucleotide sequence encoding an assayable marker peptide and within the splice acceptor and splice donor sites. Jarvik et al do not specifically teach the use of retroviruses to deliver the CD-DNA construct. Jarvik et al do not specifically teach the use of statistical methods to identify proteins whose levels change among the test and reference groups. Jarvik et al do not specifically teach the sorting of cells into monoclonal subgroups of genetically identical cells or oligoclonal subgroups of cells based on their differential levels of expression of the marker peptide.

Smith teaches a mini-exon comprising in a 5' to 3' orientation: i) a splice acceptor consensus sequence (3'CS), (ii) the sequence GAGG, a sequence complementary to the MnlI type IIS restriction enzyme recognition sequence, (iii) an oligonucleotide encoding a myc epitope, (iv) the sequence CCTC, a MnlI type IIS restriction enzyme recognition sequence, and (iv) a splice donor (5'CS) (e.g. Figure 1; paragraph bridging pages 117-118). Further, Smith suggests the use of the mini-exon as a tool for gene discovery by placing the mini-exon into introns in a random fashion using retroviruses or bacterial transposons, which would permit the

facile detection of proteins. Smith teaches that the mini-exon has the advantage of allowing greater speed of screening for new genes.

The 1996 New England Biolabs, Inc. Catalog (page 39) is cited only to show that the recognition sequence for MnlI is 5'-CCTCNNNNNNN-3'.

Keeton et al teach that scientists in all fields of research constantly encounter the same fundamental question—whether deviations that they observe in their experimental results occur by chance or are significant. Keeton et al teach that scientists cannot rely upon a guess and must use a system of standards based upon the mathematical probability that any observed deviation in their sample could have occurred by chance alone. Keeton et al teach that this type of analysis is called statistical analysis (page 441).

Whitney et al teach the tagging of proteins using a construct comprising a splice acceptor and splice donor flanking a nucleic acid encoding a protein with beta-lactamase (BL) activity (e.g. column 12, lines 8-65; Example 1, especially BLEC-3). Whitney et al teach the production of a library of clones, which are separated into two pools by fluorescence activated cell sorting (FACS) using the FRET system: an expressing pool (blue cells) and a non-expressing pool (green cells) to form oligoclonal subgroups based on their differential expression of the marker peptide BL (e.g. paragraph bridging columns 16-17). Further, Whitney et al teach the arrangement of the cells as a panel of single clones (monoclonal) or multiple clones (oligoclonal) (e.g. column 18, lines 41-45). The panels may be used to test compounds by treating the cells and isolating cells by FACS that have up- or down-regulation of gene expression (e.g. paragraph bridging columns 2-3; column 18, line 58 to column 19, line 35). Whitney et al teach that the use of the BL coding sequence is advantageous, because they disclose membrane permeant

substrates that allow measurement of BL activity in living cells, which allows functional screening immediately after the rapid identification of a functionally active portion of a genome, without the necessity of transferring the identified portion of the gnome into a secondary screening system (e.g. column 2, lines 16-39).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of protein tagging of Jarvik et al to include a retrovirus comprising the mini-exon cassette taught by Smith as the CD-DNA construct because Jarvik et al teach it is within the ordinary skill in the art to use a virus to deliver a variety of sequences that can be identified and used by one skilled in the art, and Smith suggests the use of the mini-exon for random protein tagging. Further, it would have been obvious to one of skill in the art at the time the invention was made to modify the method of protein tagging of Jarvik et al to include the statistical analysis of the differences between the test and reference groups as taught by Keeton. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include the BL coding sequence taught by Whitney et al into the construct of Smith, because Smith and Whitney teach constructs comprising a splice acceptor and splice donor flanking a reporter sequence. It would have been obvious to one of ordinary skill at the time the invention was made to include the sorting of cells into monoclonal or oligoclonal populations as taught by Whitney et al because Jarvik et al and Whitney et al teach the analysis of the effect of test compounds on tagged cells.

One would have been motivated to make such a modification in order to receive the expected benefit of providing a specific sequence to be used in the method, which would be required to actually carry out the method taught by Jarvik, and to provide facile detection of

proteins and a faster identification of new genes as taught by Smith. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention. One would have been motivated to include statistical analysis of the data in order to receive the expected benefit of determining whether the result occurred by change or is statistically significant as taught by Keeton et al. One would have been motivated to include the BL coding sequence and sorting of cells as taught by Whitney et al to be able to identify specific cells by using a permeant substrate that allows measurement of BL activity in living cells, which allows functional screening immediately after the rapid identification of a functionally active portion of a genome, without the necessity of transferring the identified portion of the gnome into a secondary screening system

Claims 1, 11, 12 and 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hopkins et al (WO 00/56874, cited as reference B3 on the IDS filed 7/6/2004; see the entire reference) in view of Smith (BioTechniques, Vol. 23, No. 1, pages 116-120; see the entire reference), as evidenced by the 1996 New England Biolabs, Inc. Catalog, page 39. This rejection was made in the Office action mailed 11/2/2006 and is reiterated below.

Hopkins et al teach a method for determining gene expression comprising the steps of (1) contacting a cell with a recombinant retrovirus containing in a 5' to 3' orientation (i) a branch-point sequence, (ii) a polypyrimidine tract, (iii) a splice acceptor, (iv) a nucleic acid sequence encoding a reporter, (v) a splice donor, and (vi) viral long-terminal repeats, (2) identifying cells that have integrated the cassette and express the reporter polypeptide, and (3) cloning the gene

into which the virus integrates by using 5'- or 3'-RACE (e.g. paragraph bridging pages 15-16; page 13; Figure 2B). Hopkins et al teach that the reporter gene can be followed by a stop signal or can be allowed to fuse with the coding sequence of the downstream exon, which may produce a functional protein (e.g. page 10, lines 11-16). Regarding the reporter, Hopkins et al teach that it can be a peptide epitope such as a FLAG, HA or myc epitope, which can be detected by western blot analysis with an antibody that allows detection of enzymatic activity or fluorescence upon interaction of the antibody with the epitope peptide (e.g. paragraph bridging pages 15-16). The initiation codon is provided by the endogenous gene interrupted by the retroviral vector (e.g. page 10, lines 11-16).

Hopkins et al do not teach the sequence of a CD-DNA construct containing (i) a complementary sequence of a first type IIS restriction enzyme recognition sequence and (ii) a second type IIS restriction enzyme recognition sequence, where the sequences are placed on either sited of the nucleic acid sequence encoding an assayable marker peptide (reporter) and within the splice acceptor and splice donor sites

Smith teaches a mini-exon comprising in a 5' to 3' orientation: i) a splice acceptor consensus sequence (3'CS), (ii) the sequence GAGG, a sequence complementary to the MnlI type IIS restriction enzyme recognition sequence, (iii) an oligonucleotide encoding a myc epitope, (iv) the sequence CCTC, a MnlI type IIS restriction enzyme recognition sequence, and (iv) a splice donor (5'CS) (e.g. Figure 1; paragraph bridging pages 117-118). Further, Smith suggests the use of the mini-exon as a tool for gene discovery by placing the mini-exon into introns in a random fashion using retroviruses or bacterial transposons, which would permit the

facile detection of proteins. Smith teaches that the mini-exon has the advantage of allowing greater speed of screening for new genes.

The 1996 New England Biolabs, Inc. Catalog (page 39) is cited only to show that the recognition sequence for MnlI is 5'-CCTCNNNNNNN-3'.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Hopkins et al to include the mini-exon taught by Smith either with or without the addition of a stop codon to the end of the myc epitope because Hopkins et al teach it is within the ordinary skill in the art to use a vector construct comprising each of the features disclosed by Smith et al but do not provide a specific sequence and Smith et al teach the sequence of a mini-exon that includes the splice acceptor, reporter and splice donor sequences taught by Hopkins et al.

One would have been motivated to make such a modification in order to receive the expected benefit of using the mini-exon of Smith et al to identify the random insertions of the retroviral vector in a facile manner with a greater speed of screening as taught by Smith et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

With respect to the rejection of claims 1, 12 and 17-21 under 35 U.S.C. 103(a) as being unpatentable over Jarvik et al in view of Smith, as evidenced by the 1996 New England Biolabs,

Inc. Catalog, page 39, Applicant's arguments filed 5/1/2007 have been fully considered but they are not persuasive.

The response asserts that the claims recite methods in which a protein expression profile of cells is elucidated. The response asserts that neither Jarvik nor Smith discloses or suggests a method of elucidating a protein expression profile. In response to applicant's arguments, the recitation "elucidating a protein expression profile" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

The response asserts that restriction of the Smith construct with a type IIS restriction enzyme cuts the myc exon into pieces and destroys the marker so that the Smith marker cannot be assayed after the restriction. The response asserts that the claimed invention results in an intact assayable marker after restriction with a type IIS restriction enzyme and can be detected by assays described in the specification. This is not found persuasive, because the rejected claims only require the presence of a complementary sequence of a first type IIS restriction enzyme recognizing sequence, and a sequence of a second type IIS restriction enzyme recognition sequence. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., cleavage with a type IIS restriction enzyme and subsequent detection of an intact assayable marker peptide) are

not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The response asserts that the Smith construct cannot be used to identify the exons that are fused to the myc epitope and does not render the instant claims obvious. Applicant's arguments of inoperability are based upon the location and orientation of MnlI restriction sites in the Smith construct, which do not allow obtaining information about the nucleotide sequence derived from cellular exons fused to the exon during RNA splicing. This is not found persuasive, because the rejected claims do not require the use of a type IIS restriction enzyme, such as MnlI, to identify the nucleotide sequence of the cellular exons fused to the exon during RNA splicing. Jarvik teaches that the sequence can be identified using standard methods (e.g., column 9, lines 40-60). Applicant has not provided evidence that the MnlI sites interfere with standard methods of identifying the targeted sequence (e.g., inverse PCR, Alu-PCR or ligation-mediated PCR and sequencing).

The response notes that claim 1 is directed to a construct in which restriction recognition sites flank the assayable marker. The response asserts that neither Jarvik nor Smith disclose constructs that include an assayable marker that is flanked by RE IIS sequences. This is not found persuasive, because Smith teaches a construct where MnlI type IIS restriction enzyme recognition sequences flank an oligonucleotide encoding a myc epitope (see Figure 1A, GAGG type IIS sequence in line 2, Myc epitope in lines 3-4, and CCTC type IIS sequence in line 5).

The response asserts that Jarvik does not provide a method to retrieve sequence information from the tagged proteins or the gene to which the reporter is fused. This is not found

persuasive. Jarvik teaches the identification of the genes and proteins using standard methods (e.g., column 9, lines 40-61). Further, the response asserts that Jarvik does not teach the type IIS restriction sites. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The type IIS restriction sites are taught by Smith. The response asserts that Jarvik does not describe the method of SAVI to retrieve sequence tags. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the use of SAVI to retrieve sequence tags and the genomic site of integration) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The response asserts that the miniexon described by Jarvik does not contain Type IIS restriction sites in the proper orientation to capture upstream and downstream sequence tags that reveal the identity of the cellular exon directly fused to the reporter exon. The response asserts that Jarvik would need cloning of individual cells showing expression of the reporter protein and performing a separate analysis of the protein tagged and gene integration site of each clone. These arguments are not found persuasive, because the claims read on such a process. The claims only require "determining the identity of the proteins to which the marker peptide is fused in each group of cells." The rejected claims do not set forth specific positive action method steps for the determining process. Thus, the process described by Applicant as being necessary to

determine the identity of the proteins falls within the scope of what is claimed. Further, the response asserts that Applicant's method allows the simultaneous identification of integration sites from multiple mixed clones; however, the steps necessary to differentiate Applicant's invention from the teachings of Jarvik et al and Smith are not present in the claims.

The response asserts that Jarvik does not classify the population of gene trapped cells in subpopulations of cells based on the level of expression of the reporter gene. This is not found persuasive, because this is not a limitation of the rejected claims (claim 1 or claims that depend therefrom).

The response asserts that Applicant's method classifies the population of cells in separate subpopulations based on the level of expression, followed by analysis of all sequence tags present in each subpopulation in order to identify the individual levels of gene trapping present in each and every one of the separated subpopulations, which allows one to reconstruct the "distribution profile of protein expression" or "protein expression profile" for each fusion present in different subclones with a mixed population of clones. In response to applicant's arguments, the recitation "elucidating a protein expression profile" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 1, 12, 14, 15 and 17-21 under 35 U.S.C. 103(a) as being unpatentable over Jarvik et al in view of Smith and further in view of Morin et al, as evidenced by the 1996 New England Biolabs, Inc. Catalog, page 39, Applicant's arguments filed 5/1/2007 have been fully considered but they are not persuasive.

Applicant's comments regarding the Smith reference are not persuasive for the reasons set forth above.

The response asserts that the Morin transposon does not incorporate type IIS restriction sites that the borders of the exon to allow the recovery of sequence tags corresponding to exons fused to the GFP exon by RNA splicing. This is not found persuasive, because the type IIS restriction sites are taught by Smith (see the discussion above).

The response asserts that Morin determines the transposon insertion points by inverse PCR from genomic DNA and not RT-inverse PCR. This is not found persuasive, because the rejected claims do not require a process of RT-inverse PCR. The rejected claims are readable upon identification of insertion points by inverse PCR from genomic DNA.

The response asserts that Morin does not quantify the level of expression of the fusion protein or simultaneous characterization of multiple trapped genes and assignment of a defined level of gene expression to those genes. This is not found persuasive, because the rejected claims do not contain the argued limitations.

The response asserts that the rejected claims are directed to method of elucidating protein profiles in a cell or in a group of cells, which is not taught or suggested by the cited references.

In response to applicant's arguments, the recitation "elucidating a protein expression profile" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 1, 12, 14-21, 26 and 27 under 35 U.S.C. 103(a) as being unpatentable over Jarvik et al in view of Smith and further in view of Morin et al and Sinclair et al, as evidenced by the 1996 New England Biolabs, Inc. Catalog, page 39, Applicant's arguments filed 5/1/2007 have been fully considered but they are not persuasive.

Applicant's comments regarding Jarvik/Smith/Morin are not found persuasive for the reasons set forth above.

The response asserts that the toxicity of Aquorea GFP was not described in any of the references. This is not found persuasive. Sinclair states, "Toxicity from *Aequorea* GFP leads to problems in many cell lines, as shown by side-by-side experiments in cultured HeLa cells" (sentence bridging pages 1/3 to 2/3). The absence of reported toxicity in mice would not dissuade one of ordinary skill in the art from using a humanized GFP protein in a human cell line.

The response asserts that the rejected claims are directed to method of elucidating protein profiles in a cell or in a group of cells, which is not taught or suggested by the cited references. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., elucidating protein expression profiles in cells or groups of cells) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 1, 2, 12 and 17-21 under 35 U.S.C. 103(a) as being unpatentable over Jarvik et al in view of Smith and further in view of Keeton et al, as evidenced by the 1996 New England Biolabs, Inc. Catalog, page 39, Applicant's arguments filed 5/1/2007 have been fully considered but they are not persuasive.

The response asserts that Jarvik does not disclose or suggest specific methods of identifying a CD-tagged protein. This is not found persuasive, because the claims do not require a specific method of identifying the tagged proteins.

The response asserts that the claimed invention differs from the teachings of the references, because the instant invention allows testing the effect of a drug on multiple genes at the same time by sorting cells into subpopulations of cells according to the levels of expression of the tagged proteins, and then analyzing the identity of the genes and comparing the level of expression of multiple genes derived from a population of non-treated cells with the level of expression of multiple genes derived from a population of treated cells. In response to

applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., sorting cells into subpopulations of cells according to the levels of expression of the tagged proteins) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The response asserts that claim 2 does not refer to statistical methods and thus cannot be obvious in view of Keeton. This is not found persuasive. Deletion of the phrase "by statistical methods" from claim 2 does not narrow the scope of the claim. Rather, it broadens the claim such that any comparing can be used, including statistical methods.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 1, 2-6, 12, 13, 17-21 and 28 under 35 U.S.C. 103(a) as being unpatentable over Jarvik et al in view of Smith and further in view of Keeton et al and Whitney et al, as evidenced by the 1996 New England Biolabs, Inc. Catalog, page 39, Applicant's arguments filed 5/1/2007 have been fully considered but they are not persuasive.

The response asserts that Jarvik, Smith and Keeton do not disclose or suggest the use of a construct in which RE IIS sites flank an assayable marker. This is not found persuasive for the reasons set forth above.

The response asserts that Whitney does not disclose or suggest a method for elucidating a protein profile in a cell or group of cells. The response asserts that Whitney only teaches the comparison of the same population of cells before and after the treatment of the cells with a drug

or stimulus. The response asserts that the teachings of Whitney differ from the invention of the instant application in that Applicant's invention allows the comparison of two separate populations of cells, either obtained before or after the treatment with a drug or two populations of completely different origins. The response provides an example where the instant invention can be used to compare the expression profiles of normal cells with cancer cells from the same or different tissue type. The response asserts that this comparison cannot be determined by the method of Whitney, because it is not possible to induce the transition of a tumor population of cells to a normal non-transformed phenotype or visa versa upon a stimulus. Further, the response asserts that Whitney only teaches the analysis of a portion of the proteome, whereas Applicant teaches the whole tagged proteome. This is not found persuasive, because these asserted differences do not specifically relate to the claimed invention. Claim 28 is directed to a method of screening for small molecule drugs, comprising the steps of (i) generating cells by using methods of claims 1, 2, 3, 4, 5 or 6; (ii) selecting cells which have integrated the marker peptide into a locus coding a protein for which a small molecule drug is to be identified; (iii) establishing a monoclonal cell line from cells of step (ii); and (iv) screening the cell line of step (iii) against libraries of drug compounds to identify compounds which decrease expression of the marker polypeptide by means of inhibiting expression of the protein to which the marker polypeptide is fused. Both Jarvik et al and Whitney et al teach methods of screening. Whitney et al specifically teach methods of establishing monoclonal cell lines, and screening compounds that inhibit expression of a protein (e.g., Figure 1; column 15, lines 16-22). The claimed method of screening does not require screening in two populations of completely different origins. Claim 28 depends from claim 1, which does not require two different populations of cells. Claim

28 does depend from claim 2, which involves two populations of cells; however these populations are not of completely different origins as suggested by Applicant. The cells of both populations are obtained by introducing the same vector into the cells. Thus, there is no clear difference between the two populations of cells. The reasons set forth in the response do not clearly distinguish the claimed invention from the combined teachings of Jarvik et al, Smith, Keeton et al, and Whitney et al.

The response asserts that Applicant's invention allows the comparison of an expression profile without subjecting the population to a stimulus. The teachings of Whitney directed to the application of a stimulus are applied to rejected claim 28, which is drawn to screening the cells against drug compounds. Thus, the claims require the administration of a stimulus as a drug compound. Whitney also teach the sorting of cells into a monoclonal subgroup or an oligoclonal subgroup prior to the administration f a stimulus (e.g., Figure 1), which teachings are applied to claims 3-6 and 13.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 1, 11, 12 and 17-21 under 35 U.S.C. 103(a) as being unpatentable over Hopkins et al in view of Smith, as evidenced by the 1996 New England Biolabs, Inc. Catalog, page 39, Applicant's arguments filed 5/1/2007 have been fully considered but they are not persuasive.

The response asserts that the rejected claims are method claims drawn to elucidating a protein profile in a cell or group of cells and that Hopkins does not disclose or suggest a method for elucidating a protein profile in a cell or group of cells. This is not found persuasive, because

the outcome of the method of claim 1 and claims that depend therefrom is "determining the identity of the proteins to which the marker peptide is fused in each group of cells." This is taught by Hopkins. In response to applicant's arguments, the recitation "elucidating protein expression profile" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

The response asserts that Hopkins does not disclose the construct used by the instant claims in which there are two RE IIS recognition sites flanking an assayable marker. The rejection is based upon the combined teachings of Hopkins et al and Smith. The REIIS restriction sites flanking an assayable marker are taught by Smith (e.g., Figure 1).

The response asserts that the method described by Hopkins does not involve separating the gene trapped cells in subpopulations according to the level of expression of the gene trapped protein but instead they quantify the level of expression of the gene trapped expression unit by quantitative PCR, starting from isolated cloned cells. The response also asserts that Hopkins et al do not quantify the level of expression of the fusion protein and cannot simultaneously characterize multiple trapped genes and assign a defined level of gene expression to those genes. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., separating cells based on their levels of expression, quantifying the level of expression of a fusion protein, simultaneous

characterization of multiple trapped genes where a defined level of gene expression is assigned) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

/Celine X Qian Ph.D./
Primary Examiner, Art Unit 1636